SOME *A PRIORI* PATHOMETRIC EQUATIONS.

BY

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IN the second edition of my book on the *Prevention of Malaria* (Murray, 1911) I published a considerable amount of work (which had occupied me for a long time) on what may be called pathometry—that is, the mathematical study of epidemiology. In these studies I followed the *a priori* method: in other words, I *assumed* a knowledge of the fundamental laws governing the time-to-time variations of disease in a population of living creatures; formed the corresponding difference- and differential-equations; and then sought by solving these to ascertain the more remote laws which should govern the variations if my assumptions were correct. My work was concerned chiefly with insect-borne diseases; but on page 678 I gave brief, but not quite complete, integrated equations on the general theme, these equations being obtained on the supposition that the total population remains constant during the considered period of time. A year ago, however, I was able to remove this restriction by integrating the original differential equations even when the population varies, and I have now found a simplification which enables us to state the equations in forms which are easy to analyse and which will be readily understood by any one who has some knowledge of the calculus. Thus put, they give us an elegant (though tentative) mathematical theory both of epidemic and endemic communicable diseases.

The theory is of course based upon certain probable assumptions; but its utility lies in this very point, because it enables us to test these assumptions by comparing the resulting curves with those derived from observation or statistics—a verification which cannot otherwise be obtained. My full paper on the subject is more suitable for mathematical than for medical publications; but you may possibly consent to publish the following very brief statement for the information of some epidemiologists who, I believe, will be interested in it. I will first give the identities and equations and will then add a short explanation.

1. $v = n - m + i - e$
2. $V = N - M + I - E$
3. $K = c - (v - V)$
4. $L = 1 - (N + r)/K$
5. $\frac{dx}{dt} = Kx(L - x)$
6. $\frac{dP}{dt} = vP - (v - V)Px$
7. $x = x_o \frac{L}{x_o + (L - x_o)\epsilon^{-KLt}}$
8. $P = P_o \epsilon^{vt}\left(\frac{x}{x_o}\epsilon^{-KLt}\right)^{\frac{v-V}{K}}$
9. $KLt = log_\epsilon \frac{L - x_o}{x_o} - log_\epsilon \frac{L - x}{x}$
10. $f = cx(1 - x)$
11. $\frac{df}{dt} = cKx(L - x)(1 - 2x)$
12. $\frac{d^2f}{dt^2} = cK^2x(L - x)\left\{L - 2(2L + 1)x + 6x^2\right\}$

Here t denotes the time, measured from the beginning of the inquiry; P_o is the total population at the beginning of the inquiry (when $t = o$), and P is the total population at the end of the time t. The symbols n, m, i, e denote respectively the nativity, mortality, immigration, and emigration rates per unit of time (hour, day, or week, etc.) of the unaffected population, and v is the sum of these. The capitals of the same letters in (2) denote the same rates among those of the population who are affected by the considered disease. All these quantities are taken as being constant during the inquiry,[1] but the constants of the affected population, especially the mortality, will often be different from those of the unaffected population, and V will generally be smaller than v. The symbol r denotes the proportion of the affected population who recover in unit of time, or rather who become unaffected—that is, lose infectivity and also acquired immunity. The symbol x denotes the proportion of the total population P who are affected by the disease and living at the end of the time t, and x_o is this proportion at the beginning of the inquiry when $t = o$. The symbol f denotes the current proportion of new cases to total population at the time t, and, when multiplied by P, gives the current number of new cases—that is, the curve generally shown in statistics of epidemics.

I call the important constant c the *infection rate;* and these equations are based on the assumption that each affected individual infects or reinfects c other individuals in unit of time, and that c is a constant. But some of the individuals to whom he thus gives the infection may be affected already, and we must allow for this. The actual number of affected individuals at the time t will be xP; and by supposition these will infect or reinfect cxP individuals; but of these only the ones which are not affected at the time t will be *new* cases. The actual number of new cases, F, will then be given by the proportion,

$$F : cxP :: (P - xP) : P$$

that is $F = cxP(1 - x)$. But $f = F/P$; therefore finally we get the equation (10). This equation may, however, be also deduced from the fundamental differential equations (5) and (6) described in my book. The magnitude of c, as of the other constants, will, of course, depend on the unit of time taken. It is always positive, but must not be so small as to render KL negative.

The Curve of Affected Individuals, x, is an S-shaped curve beginning at x_o when $t = o$, and approximating to a limit L when t is large. Its tangential, $\frac{dx}{dt}$, is a symmetrical bell-shaped curve with a maximum which $= \frac{1}{4}KL^2$ when $x = \frac{1}{2}L$ and $KLt = log_\epsilon \frac{L - x_o}{x_o}$. The Curve of New Cases, f, is especially important as it should agree when multiplied by P with observed curves if our assumptions are sound. It begins at a small value when x_o is small and $t = o$, and then rises more or less rapidly, reaching its maximum, $\frac{1}{4}c$, when $x = \frac{1}{2}$ and then falling again and approximating to a limit which $= cL(1 - L)$ when t is large. In this case (Type I) it has an irregular bell shape, but one which tails away more gradually than it rises. But if L is not greater than $\frac{1}{2}$, x never exceeds the value $\frac{1}{2}$ and consequently f loses this bell shape and becomes an S-shaped curve (Type II) which constantly rises towards the limit $cL(1 - L)$. The former would appear to be the curve of true epidemic outbreaks, and the latter of slowly increasing endemic maladies. In both cases the value of f when t is large expresses and explains the endemic persistence of the disease in a locality.

The curve f is also much modified if (as usual) the reversion factor r does not come into play until months or years after infection, in which case f will at first approximate very closely to the curve $\frac{dx}{dt}$ and then tail off more slowly. Moreover, the infection rate, c, may be changed by local conditions, as for instance those of climate and season, which may favour or disfavour the transference of infection from individual to individual. It is impossible to examine these and other consequences of the equations except at considerable length; but I should add that the functions are usually easy to manage in finite terms, and seem to me, judging from general knowledge both of epidemic and endemic diseases, to be likely to agree with the facts.

So far as I know, these are the first attempts to obtain *a priori* equations on the subject; but it is interesting to compare them with results obtained *a posteriori*—that is, by trying to fit functions to observed curves of epidemics. Dr. John Brownlee has published some able papers on this part of the subject. In one paper[2] he says that the late Dr. Farr had found long ago that the second difference of the logarithm of epidemic curves is a constant. From this Dr. Brownlee deduces for epidemics a normal curve of probability (Type IV), *which is also a bell-shaped curve*, and he proceeds to fit this, with considerable success, to many epidemics. As a result he appears to conclude (page 516) that an epidemic depends on the acquisition by the infecting organism "of a high grade of infectivity at the point where the epidemic starts, this infectivity being lost from that period, till the end of the epidemic." In a

later paper[3] (page 2), in commenting upon the symmetry observed in certain epidemic curves, he says that "The deduction from this phenomenon is direct and complete—namely, that the want of persons liable to infection is not the cause of the decay of the epidemic. On no law of infection which I have been able to devise would such a cause permit of epidemic symmetry." I have not seen his studies referred to in this last sentence, but may point out that my equation (10) gives an almost completely symmetrical curve if P is nearly constant and L approximates to unity; that is, when N and r are small and c is large; that is, when the epidemic is short and sharp—just in such cases as those which Dr. Brownlee refers to. I am also inclined to doubt on biological grounds whether infectivity can be increased and diminished by any act, so to speak, of the infecting organism itself, but am much more disposed to think that the infection rate may be altered by local conditions, such as those of environment and climate. It seems also likely that epidemics in certain diseases may be due to a previous lowering by chance of the constant of endemicity in the population concerned, followed by a chance increase of affected immigration. I am, however, by no means prepared to contest Dr. Brownlee's very valuable results until some attempt has been made to fit my curves to known cases. The whole subject appears to me to be of such interest and importance that I have ventured to write a somewhat long letter upon it.

REFERENCES.

[1] See *Prevention of Malaria*, p. 658 et seq. [2] *Proceedings of the Royal Society of Edinburgh*, 1907, vol. xxvi, Part VI. [3] *Proceedings of the Royal Society of Medicine*, June, 1909.

Memoranda:

MEDICAL, SURGICAL, OBSTETRICAL.

A NOTE ON THE BACTERIOLOGY OF TWO CASES OF ULCERATIVE STOMATITIS.

ALTHOUGH the infectious nature of ulcerative stomatitis in children has been recognized for a long time, little as to the nature of the organisms causing the disease has been published. Bernheim and Popischill[1] described a diphtheroid bacillus and a spirochaete in 30 cases examined; but J. G. Turner,[2] writing on the subject more recently, states that the nature of the causative micro-organism is uncertain.

In view of the scanty information available, it has been thought worth while, therefore, to record the bacteriological findings in two cases lately examined. The patients were two boys, both aged 8 years, who sat near one another in the boys' department of a London elementary school. Both children were fairly well nourished, and were apparently in good health prior to the attack of stomatitis. In the first case there was severe ulceration of the gums on both sides of the lower jaw, and of the adjacent inner surface of the cheeks. The ulceration was accompanied by the usual fetor of the breath, enlarged glands, and considerable constitutional disturbance. Shortly after the first boy was seen, the second was found to be similarly affected; but in his case the ulceration was confined to the left side of the mouth, and neither the local condition nor the general symptoms were as severe as in the other case. Swabs were taken from the deepest parts of the ulcerated surface in the side of the cheek, and in each case a streptococcus was obtained in pure culture, except for one or two colonies of *Staphylococcus albus*. The streptococcus corresponded in its morphological and cultural characteristics with *Streptococcus pyogenes*, cultural characters differentiating it clearly from *Streptococcus salivarius* of the healthy mouth. Broth cultures showed long chains of cocci, with branching arrangement; there was slight growth on gelatine at 22° C.; milk was rendered acid, but was not curdled. Animal inoculation tests were carried out, unfortunately, only after the two strains had been subcultured repeatedly. Two rabbits were apparently unaffected after intraperitoneal injection with three days old broth cultures.

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[1] Bernheim and Popischill, *Jahrbuch f. Kinderheilk.*, vol. xlvi, p. 434.
[2] Turner, *Science and Practice of Dental Surgery*, chap. xlix, 1914.

SERUM SICKNESS AND ANAPHYLAXIS.

I HAD occasion recently to give a prophylactic injection of diphtheria antitoxin to a healthy man, aged 35. He had never had any previous inoculation in the accepted sense of the word, but ten years ago he had been revaccinated during an epidemic of small-pox. The serum used was one of the well-known brands, the dose the ordinary prophylactic one of 1,000 units, and the injection was given under strictly aseptic conditions.

Immediately after withdrawing the needle, I was proceeding to apply a dressing to the site of the puncture when the patient became very pale and fell forward out of his chair, uttering a groan not unlike the epileptic cry. There were convulsive movements of the face and jaw, slightly stertorous breathing, complete loss of consciousness, with widely dilated pupils, livid complexion, and cyanosis of the ears and finger tips. After a few seconds he partially regained consciousness, and showed signs of becoming rather voluble, trying to talk and laugh loudly; then he quickly relapsed into a state resembling that of severe shock, with a profuse perspiration and a pulse-rate of only 20. At one time the radial pulse was quite imperceptible. After energetic treatment, persisted in for an hour or more, he at length began to respond, and eventually became more or less himself again, though naturally rather shaky.

All he remembered of the early stage was a feeling of annoyance at being roused out of pleasant dreams. There were no local signs such as oedema at the site of inoculation.

Is one to conclude that this alarming train of symptoms was due merely to nervous shock in a possibly "highly strung" subject, or should one regard it as a case of true anaphylaxis? If the latter, then is it possible that ordinary vaccination with calf lymph may in certain individuals have a similar effect to that of horse serum in inducing a condition of hypersensitiveness to any future inoculation?

Hale, Cheshire. W. TURNER, M.B.

Reports of Societies.

THE ROYAL SOCIETY.

Thursday, March 11th, 1915.

Sir WILLIAM CROOKES, O.M., President, in the Chair.

Restoration of Paralysed Muscles by Means of Nerve Anastomosis.

PROFESSOR R. KENNEDY'S third contribution on this subject dealt with the anastomosis of the brachial plexus, and included a consideration of the distribution of its roots. The experiments recorded consisted of division of one or more roots of the brachial plexus, and anastomosis of the divided root or roots either to another part of the plexus or to the spinal accessory. Restoration of function took place, and physiological examinations showed that this was due to the nerve which was substituted for the severed roots. When less than two roots were divided restoration of function took place much earlier, and was shown to be a spontaneous recovery due to the affected muscles being each supplied through more than one root. The distribution of the roots of the plexus was also considered, and the results of the stimulations of six plexuses in man were compared with the same number of examinations in Macacus, the comparison showing a close similarity between the two.

Mechanism of the Cardiac Valves.

Professor A. F. S. KENT presented a preliminary communication dealing with the structure and mode of action of the auriculo-ventricular valves of the mammalian heart. Muscular tissue derived from the auricular wall ran for a considerable distance into the substance of the valve flaps, being situated principally towards their auricular surfaces. It was permissible to conclude that this muscle exercised an important function in connexion with the closure of the valves. Receiving its stimulus from the base of the auricle, of which it was indeed an extension and with which it was directly connected, it came into action at the appropriate moment in the cardiac circle, and contracted (and remained contracted) last of all the auricular muscle.